REMARKS

Upon entry of the foregoing amendment, Claims 92, 94, 96, 98-101, 105, 106, 109 and 115-119 will remain pending in the application. Claims 1-91, 93, 95, 97, 102-104, 107-108 and 110-114 have been canceled. Claims 92, 96, 100 and 109 have been amended. Claims 115-119 have been added. Claims 115-119 are supported by the specification at page 25, lines 25-27 wherein states: "one of ordinary skill in the art will appreciated that a tissue-specific promoter for use in the AAV vector may be selected form any of the known liver specific promoter." No new matter has been introduced. Allowance of all pending claims in view of the following remarks is respectfully requested.

In the Office Action of February 19, 2003 and the Advisory Action of September 9, 2003, the Examiner set forth a number of grounds for objection and rejection. These grounds are addressed individually and in detail below.

Claim objections

Claim 109 stands objected for improper grammar. Applicants have amended Claim 109 to avoid the use of "and/or" in the claim. This ground of objection has been obviated.

Rejections Under 35 U.S.C. § 112, First Paragraph

Written description

Claims 92-99, 107, and 109-114 stand rejected under 35 U.S.C. §112, first paragraph, for lack of written description support in the originally filed specification for reasons set forth on pages 2 and 3 of the Office Action. With regard to Claims 92-99 and 109-114, the Examiner alleges that the specification only support a method or a pharmaceutical composition for treating hemophilia B with rAAV particles containing Factor IX coding sequence. (see page 2, last

paragraph and page 3, first paragraph of the Office Action).

Applicants have amended independent Claims 92 and 109 to restrict the present invention to the treatment for hemophilia B with rAAV particles containing Factor IX coding sequence, which is supported at page 13, lines 9-14, page 18, line 29 to page 19, line 16 of the present specification.

The Examiner also alleges that there is no general teaching of including an IVS or splice donor or acceptor site, as claimed in Claims 107 and 109-114. Applicants respectfully disagree in that the specification teaches an IVS or splice donor or acceptor site at least on page 33, lines 9-10. However, in the interest of expediting the prosecution of this case, Applicants have amended the claims consistent with the Examiner's suggestion.

Applicants have canceled Claim 107 and have amended independent Claim 109 to delete the term "an IVS", "or splice donor" and "or acceptor site".

The Examiner further alleges that Claims 109-114 fail to recite any relationship between the structure gene, the promoter, and the enhancer.

Applicants respectfully submit that the claims state that sequence encoding Factor IX is "operably linked" to the promoter. In addition, Applicants have amended independent Claim 109 to better define the relationship between the structure gene and a regulatory element. The amended Claim 109 reads "A pharmaceutical composition for treating hemophilia B comprising (a) recombinant adeno-associated virus (rAAV) particles consisting essentially of AAV terminal repeats flanking an MFG promoter, a polynucleotide encoding Factor IX operably linked to the MFG promoter, a bovine growth hormone polyA sequence, and (b) a pharmaceutically acceptable carrier." The support for the amended Claim 109 can be found, for example, on pages 24-26, 31-32 and Fig. 6 of the present specification.

Therefore, the amendment of Claims 92 and 109 and the cancellation of Claim 107 completely addresses the stated grounds of rejection. The rejection of Claims 92-99, 107, and 109-114 for lack of written description should be withdrawn.

Enablement

Claims 92-114 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement for the reasons set forth on pages 3-13 of the Outstanding Office Action. The Examiner alleges that Claims 92-114 are enabled only to those embodiments shown in the specification, such as the rAAV consists of terminal repeats flanking in order an MFG promoter, a Factor IX coding sequence, and bovine growth hormone poly A sequence . (See page 3, last paragraph and page 4, first paragraph of the Office Action).

Applicants disagree with the Examiner's interpretation of the scope of the invention taught by the instant application. However, in the interest of furthering prosecution of this case, Applicants have amended independent Claims 92, 100 and 109 to restrict the present invention for the treatment of hemophilia B. Applicants further amended Claims 92, 100 and 109 to direct the rAAV particles consisting of AAV terminal repeats flanking a constitutive viral promoter (Claim 92) or MFG (Claims 100 and 109), a polynucleotide encoding Factor IX operably linked to the viral promoter, and bovine growth hormone polyA sequence.

The use of constitutive viral promoters such as SV40 promoter, CMV promoter and RSV promoter were well-known to one skilled in the art at the time of the invention (See, for example, Li et al., *In Vitro Cell Dev Biol.*, 28(A):373-375, 1992; Kim et al., *Gene*, 134:307-308, 1993; Ponnazhagan et al., *J Exp Med.*, 179:733-738, 1994; Broxmeyer et al., *Ann N Y Acad Sci.*, 770:105-115, 1995; and Drazan et al., *J Surg Res.*, 59:299-304, 1995). As noted by the Examiner in the Advisory Action, the use of bovine growth hormone polyA sequence is supported by the vector of Figure 6.

Therefore, it is believed that the specification, at the time the application was filed, taught one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

Finally, the Examiner interpreted Claims 100-108 as being implicitly directed to gene therapy and alleges that the implied use of this method to evaluate AAV as a suitable gene therapeutic vector does not meet the utility requirement. Since the Examiner admits that the utility of the claimed methods for treating hemophilia B was not in question, the rejection is now moot in view of the proposed amendment.

Taken together, it is believed that this ground of rejection has been obviated, and therefore, the rejection under 35 U.S.C. 112 first paragraph should be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 96, 103, 107, 112 and 113 stand rejected under 35 U.S.C. 112 second paragraph for the reasons set forth on pages 13 to 14 of the Office Action.

Applicants have canceled Claims 103, 107, 112 and 113. Claim 96 has been amended to replace the term "the MFG promoter" with "a MFG promoter". Accordingly, it is believed that this ground of rejection has been obviated, and may properly be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 100, 101, 104 and 105-107 stand rejected under 35 U.S.C. 102(e) as being anticipated by Srivastava et al. (US 2001/0051611 A1) for the reasons set forth on pages 14 to 15 of the Office Action. Claims 104 and 107 have been canceled, and independent Claim 100 has been amended. Accordingly, Applicants respectfully traverse the rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. Verdegaal Bros. v. Union Oil Co. Of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. Scripps Clinic Research & Foundation v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

In this case, independent claim100 is directed to a method for treating hemophilia B in a mammal, comprising: administering recombinant adeno-associated virus (rAAV) particles to a mammalian liver cell, wherein said rAAV particles consist essentially of AAV terminal repeats flanking a MFG promoter, a polynucleotide encoding Factor IX operably linked to said MFG promoter, and a bovine growth hormone polyA sequence, and wherein following infection of said mammalian cell, Factor IX protein is expressed in the liver.

In contrast, Srivastava describes methods for selectively expressing therapeutic molecules in the liver. Srivastava neither describes the MFG promoter, nor mentions the specific viral construct as claimed in the present invention. Accordingly, Srivastava does not anticipate the present invention because it does not contain all of the elements of Claim 100. Applicants further submit that dependent Claims 101, 105 and 106 are not anticipated by Srivastava because they depend from Claim 100.

Thus, the grounds for this rejection have been obviated and withdrawal of the 35 U.S.C. 102(e) rejection is respectfully requested.

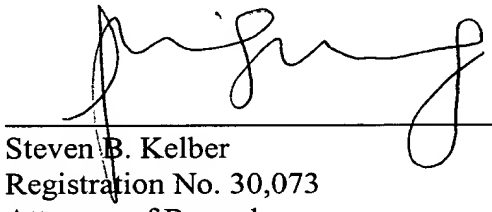
CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact Ping Wang, M.D. (Reg. No. 48,328) at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP



Steven B. Kelber
Registration No. 30,073
Attorney of Record

Ping Wang, M.D.
Registration No. 48,328

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085